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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,094	03/08/2001	Paul Calabresi	21486-038	4935

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EXAMINER

YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 06/20/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/802,094

Applicant(s)

CALABRESI ET AL.

Examiner

Christopher H Yaen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 May 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 1-8 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group II in Paper No. 12 is acknowledged. Claims 1-8 are pending, and claims 9-20 are examined on the merits.

Information Disclosure Statement

2. The IDS, paper no. 7 filed on July 18, 2001, was not found in the application. Examiner requests the submission of an additional copy of the references to be considered in the next office action, without any additional fee.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 9, 11, 14, 15, 16, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Leary *et al.* (Clinical Cancer Res. 1999 Jan; 5:181-187). Claims 9, 11, 14, 15, 16, and 20 are drawn to a method of inhibiting tumor cell growth in a mammal, comprising the administration of a compound comprising an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity, wherein the DNA topoisomerase inhibitor is a camptothecin compound, wherein the camptothecin compound is irinotecan (CPT-11) and topotecan, and wherein the compound is administered simultaneously. O'Leary *et al.* discloses

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a method of inhibiting cancer cell growth by administering a compound that can be used to inhibit both angiogenesis and DNA topoisomerase activity, therefore also a simultaneous administration, wherein the compound is a camptothecin compound that is capable of performing both desired effects. Furthermore, O'Leary *et al.* also discloses specific camptothecin molecules, including CPT-11, topotecan, and 9-AC³. Therefore, the claims as currently interpreted are anticipated by the prior art, because O'Leary *et al.* disclose of a single compound that is an inhibitor of angiogenesis and DNA topoisomerase I enzyme activity, that is able to inhibit tumor cell growth in a mammal.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 9-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Leary *et al.* in view of Sheibani *et al.* (Biochem Biophys Res commun 2000 Jan 7; 267(1):257-61,) and Streit *et al.* (Proc Natl Acad Sci USA 1999 Dec 21; 96(26):14888-93).

Claims 9-20 are drawn to a method of inhibiting tumor cell growth through the administration of composition comprising an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity, wherein the inhibitor of

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angiogenesis is a thrombospondin and the inhibitor of DNA topoisomerase I enzyme activity is a camptothecin compound.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

O'Leary *et al.* disclose of a method of inhibiting cell growth in a mammal, wherein the composition that is administered is a camptothecin compound that is capable of inhibiting both angiogenesis and DNA topoisomerase activity. In addition, O'Leary *et al.* disclose of specific camptothecin molecules that are capable of performing this function. Furthermore, O'Leary *et al.* suggests that a combination of camptothecin compounds with endogenous inhibitors of angiogenesis would improve antitumor efficacy (see page 181 (abstract), and page 186 1st column). O'Leary *et al.*, however, fails to disclose specific endogenous inhibitors of angiogenesis.

Sheibani *et al.* and Streit *et al.*, however, disclose of Thrombospondins (TSP), namely TSP-1 and TSP-2, both of which are endogenous inhibitors of angiogenesis. Sheibani *et al.* disclose the potent effects of TSP-1, an endogenous inhibitor of angiogenesis, while Streit *et al.* disclose of the potent effects of TSP-2 as a anti-tumor molecule.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to derive of a method of inhibiting cell growth through the use of a composition comprising an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity, because the prior art provides sufficient motivation to practice the invention as claimed. The suggestion or motivation for doing what the applicant has claimed is that it was already known in the art at the time the invention was made that a composition comprising an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity was available, as taught by O'Leary *et al.* Furthermore, it was also known that a combination of camptothecin, the composition taught by O'Leary *et al.* with endogenous inhibitors of angiogenesis, that a more potent effect could be achieved (O'Leary *et al.*). Still further, it was also known at the time of the invention to the skilled artisan that natural inhibitors of angiogenesis existed and being used as such had potent effects as an anti-tumor agent (see Sheibani *et al.* and Streit *et al.*). Therefore, it would have been *prima facie* obvious at the time of the invention to devise of a method of inhibiting tumor cell growth using a composition comprising an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity, because the prior art disclose all aspects of the instant invention. One of skill would be motivated to attempt the combination because the prior art suggests that success could be achieved if a combination of the separate components were added together, thereby leading to a more potent effect.

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It would also be obvious to one of ordinary skill in the art to combine two well established components in the art, that are known to be effective against cancer, to make a composition that has a greater effect, because it was already established that separately, the two components are effective, and one of ordinary skill would expect a reasonable amount of success if they were to be combined. Therefore, it would be obvious to combine TSP and camptothecin molecules to derive of a new composition comprising of the combination to be used in a method to inhibit tumor cell growth, because separately the compounds as taught by O'Leary *et al.*, Sheibani *et al.*, and Streit *et al.* all have activity in inhibiting tumors growth independently.

Conclusion

No claims allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

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Christopher Yaen
Art Unit 1642
June 14, 2002



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